# PEC UPDATE

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**DOD PharmacoEconomic Center, 2107 17th Street, Bldg 4197, Ft Sam Houston, TX 78234-5036**
**DSN: 471-4311; Commercial: (210) 221-4311: FAX Extension: 4314**
**E-Mail: hscphaec@smtplink.hcssa.amedd.army.mil HomePage: http://www.ha.osd.mil/hppec2.html#Start**


## ISSUE HIGHLIGHTS



### PEC COMPUTER BBS

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## Treatment of Vulvovaginal Candidiasis

The initial Tri-Service Formulary (TSF) was approved in November 1993. Since this time the PEC has completed six major disease state reviews resulting in changes to the TSF. The management of vulvovaginal candidiasis is the seventh disease state review conducted by the PEC resulting in changes to the TSF. This disease state review was also used as the pilot project in a joint effort between the Defense Personnel Support Center (DPSC) and the PEC to develop a new Best Value procurement process (see PEC Update 96-06, 15 March 1996). DPSC used the disease state model developed by the PEC in a Request for Proposal (RFP) submitted to the various manufacturers of the antifungals for the treatment of vaginal candidiasis. The offers that were submitted were considerably higher than the top ranked regimens based on current Distribution and Pricing Agreement (DAPA) and Federal Supply Schedule (FSS) prices. DPSC recommended that the current solicitation be canceled and that current DAPA and FSS prices be used as the basis for drug acquisition price in the model. This PEC Update includes the TSF changes, cost-effectiveness model, treatment guidelines, preferred drug list, and drug usage evaluation (DUE) criteria for the treatment of vulvovaginal candidiasis.

**Executive Summary**

*Background*

Approximately 75% of women will develop vulvovaginal candidiasis (VVC) at least once during their lifetime, and 40 to 50% of these women will experience another episode. An estimated 5 to 10 million office visits occur each year secondary to vaginal symptoms with VVC accounting for at least one-quarter of these visits. The Department of Defense (DOD) spent an estimated $2 million dollars in fiscal year 1995 on drug treatments alone for VVC.

*Materials and Methods*

A mathematical model of cost-effectiveness is employed to determine the most cost-effective treatment of an uncomplicated episode of VVC. Costs and benefits are evaluated from the perspective of the Department of Defense (DOD) as payer of the health care benefit and employer. Thirteen different antifungal regimens currently available for 1-, 3-, or 7-day treatment of VVC are included in the analysis. Nystatin is not included because of its 14-day treatment regimen, and ketoconazole and itraconazole are not included because of their limited use in the primary care setting.

The target population for this analysis is women in the Military Health Services System (MHSS) between 15 and 65 years of age. Pregnant women are not included in this analysis since these patients may require a longer duration of therapy or repeated treatment courses during their pregnancy. The model begins with a diagnosis of VVC based on clinical signs and symptoms. Three groups of women are treated: (1) those with vulvovaginal candidiasis; (2) those with vulvovaginal candidiasis and a concomitant infection; or (3) those with vaginitis not due to *Candida* species. All patients are assumed to receive a prescription for a drug product. Over-the-counter (OTC) and prescription medications are assumed to be dispensed from the military medical treatment facility (MTF) pharmacy.

Costs of treatment include drug acquisition cost and topical therapy cost for patients with vulvar involvement who receive an oral tablet or vaginal suppository/tablet, unless these agents are available in a combination kit. Adverse effects associated with the treatment regimens are minimal, and the costs to DOD are negligible, thus these are not included in the analysis. Cost of failure is included for patients not responding to treatment. The cost of a provider visit and diagnostic laboratory tests are included. Ideally, one could assume that all patients with a treatment failure will incur a cost to the system; however, with the availability of OTC preparations, some patients may not return even if they experience treatment failure. A factor is included to account for the percentage of patients who would incur a cost to the system. Because of the military perspective, the model accounts for the cost of lost productivity of female active duty personnel who require follow-up because of a treatment failure.

Short-term clinical cure, as defined by significant improvement or complete resolution of the clinical symptoms and signs of VVC, is used as the outcome measure. Based on a review of the literature, all treatment regimens are assumed to have equal efficacy when used appropriately for the recommended treatment duration. Because patients may have a clinical cure without completing a full course of therapy, the efficacy is adjusted for the compliance with each day of therapy. Additionally, patients not infected with *Candida* may have a spontaneous resolution of symptoms after treatment with an antifungal agent. All variables and their ranges are included in Table 2 in the full report. Data are obtained from published medical literature, pharmaceutical manufacturers, DOD database systems, and expert consensus. Drug acquisition prices as of May 28, 1996 were used in the model.

*Results*

A Monte Carlo analysis (multivariate sensitivity analysis) of 1000 trials was performed to measure the effects of simultaneous changes in multiple assumptions. The rank order of drug regimens by cost-effectiveness changed very little from baseline with the Monte Carlo analysis. Prevalence of the disease was the variable with the largest contribution to the variability of the model results. However, univariate sensitivity analysis with this variable and others produced no change in the overall rank order of the drug regimens.

Based on this analysis, the most cost-effective regimen is the clotrimazole 500 mg single dose vaginal tablet ($24.52/clinical cure). For patients with vulvar involvement, miconazole 2% topical cream (15 gm or 30 gm tube) should also be provided. Miconazole 2% top-ical cream was selected since it had the lowest drug acquisition cost of the available topical antifungal agents. If clotrimazole 500 mg single dose vaginal tablet does not provide a cure, the diagnosis should be reconsidered, and if candidiasis is still suspected, the patient could repeat the regimen or use the next appropriate regimen. Fluconazole, although ranked fourth overall ($29.52/clinical cure), has considerable convenience for active duty females in deployment situations, and thus, should be added, along with the Tri-Service Formulary selection, to the D-Day list of medications for deployment.

**Tri-Service Formulary Selections**

The Tri-Service Formulary (TSF) selection for the treatment of vulvovaginal candidiasis is clotrimazole 500 mg single dose vaginal tablet. Miconazole 2% topical cream is added for patients with vulvar involvement. Fluconazole is **not** recommended for addition to the TSF although it should be included on the D-Day list of medications for deployment in addition to the TSF selection.

## TSF Revisions Resulting from the Vulvovaginal Candidiasis Review

| AHFS Category* | | Action |
|---|---|---|
| ***84:04.08*** | ***Antifungals (Skin and Mucous Membrane)*** | |
| | Clotrimazole 500 mg vaginal tablets | Add |
| | Miconazole 2% topical cream | Add |

* AHFS = American Hospital Formulary Service

# Pharmacoeconomic Model for the Treatment of Vulvovaginal Candidiasis

## Introduction

Approximately 75% of women will experience vulvovaginal candidiasis (VVC) at least once during their lifetime, and 40 to 50% of these women will experience another episode.[1-3] However, less than 5% of women develop recurrent VVC (3 or more episodes annually).[2] Vaginal symptoms account for an estimated five to 10 million physician office visits each year.[4,5] If one-quarter of these visits are attributed to *Candida*, then an estimated 1.25 to 2.5 million cases of vaginal candidiasis occur each year in the United States. The Department of Defense (DOD) spent an estimated $2 million dollars on drugs alone to treat VVC in fiscal year 1995.

*Candida* species, *Trichomonas*, and bacteria are the most common causative organisms of infective vaginitis in the United States.[1,2,4,5] Symptoms and signs associated with *Candida* vulvovaginitis include vulvar and vaginal irritation, burning, itching, dyspareunia, dysuria, and a thick, white discharge. Simple diagnostic examination in patients with *Candida* infection usually reveals a normal vaginal pH ($\leq$ 4.5), a negative "whiff" test for aromatic amines in the presence of potassium hydroxide (KOH) 10%, and visualization of hyphae or spores on micros-copy with KOH preparation.[6-8] Approximately 80 to 90% of cases of VVC are caused by *Candida albicans*, with other *Candida* species accounting for the remaining cases.[2,3,6,7,9]

Several factors are associated with increased risk of vaginal candidiasis, including: (1) pregnancy; (2) diabetes mellitus; (3) recent exposure to systemic antibiotics; (4) immunosuppressant drugs (e.g., corticosteroids); or (5) immunosuppressed states (e.g., HIV infection).[1,2,6,7,10] These factors should be considered in patients who fail to respond to treatment, or return with a second infection within 2 to 3 months.[7]

Many different antifungal treatment regimens for vaginal candidiasis are currently available in the United States. Several regimens are approved for over-the-counter (OTC) use, allowing women previously diagnosed with vaginal candidiasis to initiate treatment without returning to the provider. Health care plans may or may not cover OTC products. If the OTC products are not covered, plans will usually continue to cover one or all of the legend regimens, thus potentially increasing the overall cost to the health care system through provider visit and prescription medication costs, which may exceed the costs of medications available as OTC products.

In the Department of Defense (DOD) Military Health Services System (MHSS), women have two options—purchase an OTC product at their own expense, thus incurring no cost to the MHSS, or see a military medical treatment facility (MTF) practitioner and receive a prescription for a legend or OTC product at no cost to the patient. For this latter option, a cost-effectiveness analysis was conducted to evaluate the overall costs associated with the treatment of an uncomplicated episode of vulvovaginal candidiasis within the MHSS.

## Materials and Methods

### *Model Overview*

A mathematical model of cost-effectiveness is employed in this study (Figure 1). Costs and benefits are evaluated from the perspective of the DOD as payer of the health care benefit and employer. Drug regimens currently available for the 1-, 3-, or 7-day treatment of VVC are included (Table 1). Nystatin was not included in the analysis because of its limited use since the advent of the imidazole (e.g., butoconazole, clotrimazole, miconazole, and tioconazole) and triazole (e.g., fluconazole, and terconazole) antifungal agents and its required 14-day treatment regimen.[7] Additionally, itraconazole and ketoconazole are excluded from the analysis because they are not commonly used in the primary care setting and are usually limited to resistant or recurrent cases.[7]

The analytical model begins with a diagnosis of VVC based on clinical signs and symptoms without additional diagnostic tests. Diagnostic tests such as normal saline or potassium hydroxide (KOH) preparations are performed in some settings; however, practitioners may treat despite negative test results in the absence of other apparent diagnoses[11] and are, in theory, treating based on clinical diagnosis. Cultures for *Candida* are not routinely performed, and are usually reserved for selected patients to confirm a presumptive diagnosis.[11] Approximately 30 to 50% of symptomatic women with positive yeast cultures will have negative microscopy studies.[6] Efficacy is initially determined 7 to 10 days after the start of therapy, and patients classified as failures after one course of treatment may return to the provider for further evaluation. A secondary analysis was conducted to evaluate the use of additional diagnostic testing, such as the latex agglutination test, which should increase diagnostic accuracy. Discounting was not employed due to the short treatment duration.

**Figure 1.—**Cost-effectiveness equation for vulvovaginal candidiasis model. See text for further explanation of model variables.

$$\frac{\text{Cost}}{\text{Effectiveness}} = \frac{\text{(cost of treatment) + (cost of failure) + (cost to treat side effects) + (cost of lost work)}}{\text{(probability of cure with treatment)}}$$

$$CE_A = \frac{[\ cA + cLA + (cTA \times pVI)\ ] + [\ (1 - pEff) \times (cMDV + cFLA) \times pRV\ ] + [\ HR \times cW \times (1 - pEff) \times pADF \times pRV]}{\{\ [\ \sum_1 (pE_n)(pC_n)\ ] \times (pCCD) \times (1 - pCI) + pEffP\ \}}$$

cost of treatment$_A$ = cA + cLA + (cTA × pVI)

cost of failure = (1 – pEff) × (cMDV + cFLA) × pRV

cost to treat side effects = no cost incurred to MHSS

cost of lost work = (HR) × (cW) × (1 – p Eff) × (pADF) × pRV

$$\text{Probability of Candida with clinical diagnosis (pCCD)} = \frac{(Pr)(Se_{CD})}{(Pr)(Se_{CD}) + (1 - Pr)(1 - Sp_{CD})}$$

Probability of clinical cure if Candida not present (pEffP) = (pSR) × (1 – pCCD)

Probability of clinical cure with treatment (pEff) = $[\ \sum_1 (pE_n)(pC_n)\ ] \times (pCCD) \times (1 - pCI) + pEffP$

**Variable Definitions**

cA = cost of drug A
cFLA = cost of labs for failure of drug A
cLA = cost of initial labs for drug A
cMDV = cost of second MD visit
cTA = cost of topical treatment along with drug A
cW = hourly wage of female active duty personnel
HR = hours lost from work to return to MD due to failure
pADF = probability of the patient being an active duty female
$pC_n$ = probability of completing day *n* of treatment
pCCD = probability of a correct clinical diagnosis
pCI = probability of having Candida and concomitant infection
$pE_n$ = probability of efficacy for treatment of *n* day duration
pEff = probability of clinical cure with treatment
pEffP = probability of clinical cure with placebo in a patient with symptoms consistent with vulvovaginal candidiasis, but not infected with Candida
Pr = prevalence of vaginal candidiasis among women with symptoms
pRV = probability of a return visit if symptoms fail to improve
pSR = probability of spontaneous resolution of clinical symptoms in a patient who is not infected with Candida, but is given a diagnosis of vaginal candidiasis
pVI = probability of vulvar involvement
$Se_{CD}$ = sensitivity of clinical diagnosis for vaginal candidiasis
$Sp_{CD}$ = specificity of clinical diagnosis for vaginal candidiasis

***Treated Groups***

Because signs and symptoms may not be predictive of *Candida* infection[13-15] when considering the clinical diagnosis of VVC, three situations are possible: (1) correct diagnosis is made; (2) correct diagnosis is made, but a concomitant infection is not diagnosed; or (3) incorrect diagnosis is made. Since all three of these situations will be treated by the clinician as presumed VVC, the model had to include all three possibilities. Based on these possibilities persons treated are grouped into three categories: (1) vulvovaginal candidiasis; (2) vulvovaginal

**Table 1.—**Regimens for treatment of vulvovaginal candidiasis included in the cost-effective-ness analysis.

| Regimen* | Duration, days | Pregnancy Category[12] | Rx/OTC Status |
|---|---|---|---|
| Clotrimazole 500 mg vaginal tablet | 1 | B | Rx/OTC |
| Clotrimazole 500 mg vaginal tablet + topical cream kit | 1 | B | Rx/OTC |
| Fluconazole 150 mg oral tablet | 1 | C | Rx |
| Tioconazole 6.5% vaginal ointment | 1 | C | Rx |
| Butoconazole 2% vaginal cream | 3 | C | Rx/OTC |
| Clotrimazole 200 mg vaginal tablets† | 3 | B | OTC |
| Miconazole 200 mg vaginal suppositories | 3 | B | Rx |
| Miconazole 200 mg vaginal suppositories + topical cream kit | 3 | B | Rx |
| Terconazole 80 mg vaginal suppositories | 3 | C | Rx |
| Terconazole 0.8% vaginal cream | 3 | C | Rx |
| Clotrimazole 100 mg vaginal tablets | 7 | B | OTC |
| Clotrimazole 1% vaginal cream | 7 | B | OTC |
| Miconazole 100 mg vaginal suppositories | 7 | B | OTC |
| Miconazole 2% vaginal cream | 7 | B | OTC |
| Terconazole 0.4% vaginal cream | 7 | C | Rx |

* All suppository or oral therapy regimens must have a topical cream dispensed separately if required for treatment of vulvar involvement. Miconazole 2% topical cream (15 gm or 30 gm tube) was included as topical therapy when required.

† Two 100 mg vaginal tablets are used for this regimen.

candidiasis and a concomitant infection; or (3) vaginitis not due to *Candida* species (Figure 2).

Vaginal Candidiasis (True-Positive Clinical Diagnosis)

The percentage of patients with a clinical diagnosis who actually have VVC is determined from the positive predictive value of the clinical diagnosis (pCCD). As noted in Figure 1, pCCD accounts for the prevalence of the disease (Pr) and the sensitivity ($Se_{CD}$) and specificity ($Sp_{CD}$) of the clinical diagnosis. Ten studies were identified that addressed the prevalence of vaginal candidiasis among patients with symptoms of vaginitis.[5,8,13-20] These studies represent a variety of clinical practice sites and different points in time. A median prevalence of 24% was used in the analysis. A clinical diagnosis has a median specificity of 80.5% and a sensitivity of 77.35%[17,21]; a range of rates was incorporated into the sensitivity analysis (Table 2).

Vaginal Candidiasis and Concomitant Infections (pCI)

A small percentage of patients correctly diagnosed with vaginal candidiasis are also infected with other organisms.[8,14,18,22-24] All patients with concomitant infection were assumed to be treatment failures due to the concomitant infection.

Vaginal Symptoms Not Caused by Vaginal Candidiasis (False-Positive Clinical Diagnosis) (pEffP)

In addition to the patients accurately diagnosed with vaginal candidiasis, some patients are clinically diagnosed with vaginal candidiasis, but do not have *Candida* species (overdiagnosis of vaginal candidiasis). It could be assumed these patients would not benefit from treatment for a disease they do not have, and thus continue to consume further resources. However, spontaneous resolution of clinical symptoms (pSR) or a placebo response to the treatment may occur in a portion of these patients, perhaps due to alterations of the vaginal flora or pH,[25,26] or due to the self-limiting nature of the infection.[10,27] The clinical cure rates of placebo creams/ ointments in bacterial vaginitis studies were used to estimate the spontaneous resolution of symptoms. A median spontaneous resolution rate of 25% is used in the model.[25,26,28-34]

### *Effectiveness*

Outcome Measure (pEff)

Clinical outcomes in the clinical trials were evaluated between 5 and 10 days after the start of treatment (short-term clinical outcome), and classified as a cure or failure. A cure is defined as significant improvement or complete resolution of the clinical symptoms and signs of VVC. Although clinical studies include data on mycologic cure rates, pre- and post-treatment cultures are not routinely preformed in a clinical setting and are not included as an outcome measure in the analysis. A clinical failure includes persons with continued symptoms after treatment. Treatment failures would include the following: (1) persons with vaginal candidiasis that failed to respond to treatment; (2) persons with cured vaginal candidiasis, but with continued symptoms due to a concomitant infection; and (3) persons not infected with *Candida* in whom clinical symptoms persisted (Figure 2).

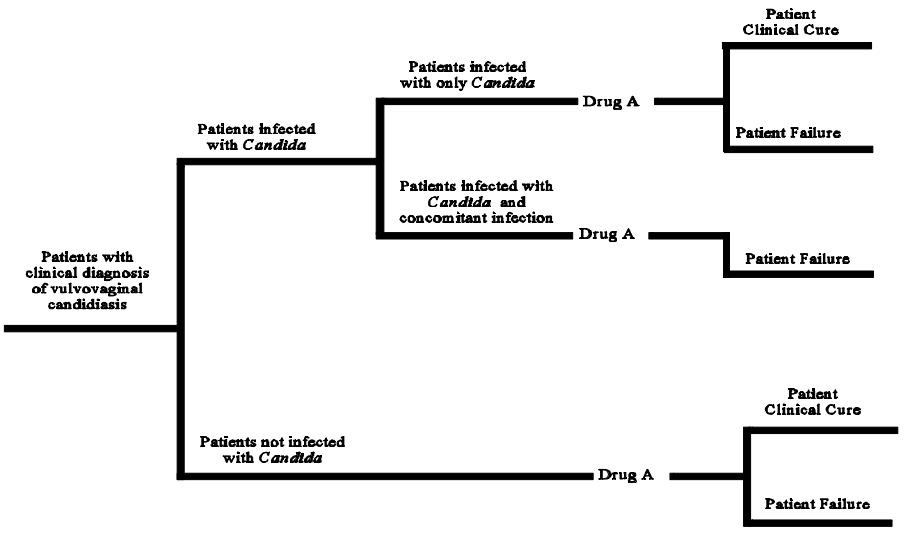


**Figure 2.—**A diagram of the patient groups included in the vulvovaginal candidiasis model. All patients have a clinical diagnosis of vulvovaginal candidiasis and receive treatment. Patients have either a clinical cure or failure. All patients with *Candida* and concomitant infection are assumed to fail therapy because of the concomitant infection.

Eligibility for Cure

The model assumes that only patients infected with *Candida* are eligible for a cure with drug therapy. However, as previously mentioned, spontaneous resolution of symptoms may occur during the treatment period in patients not infected with *Candida* species.

Efficacy of Agents

Published, randomized, controlled, single and double blind, and open clinical trials and review articles for the treatment of vaginitis and vaginal candidiasis were identified through a MEDLINE search

(1966 to November 1995). Additional studies were identified through bibliographies of selected articles and manufacturer medical information. Only studies using product formulations currently available in the United States were reviewed. At least one published report was found for each of the regimens. Forty-six studies describe short-term clinical endpoints representing 69 treatment arms.[22,35-78] Only two published studies[52,75] report significant differences in efficacy between antifungal agents. The remaining studies reported no significant differences in efficacy, nor was the efficacy affected by decreased treatment duration accompanied by increased dosages. The model assumes that all agents are equally efficacious when used appropriately for the recommended treatment duration. A median efficacy of 92.85% was used in the model (Figure 3).

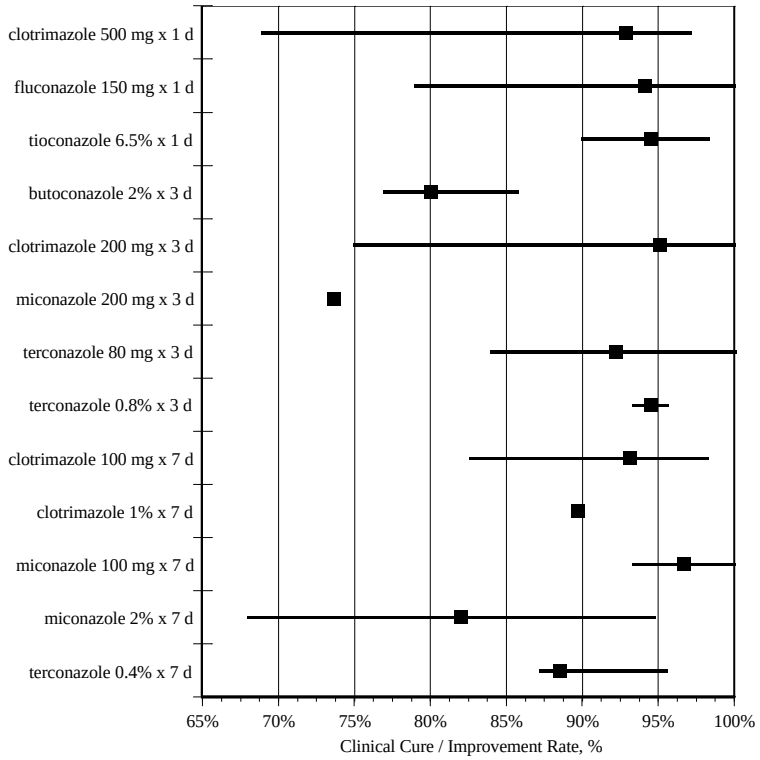


**Figure 3.—**Range of short-term clinical cure or improvement rates as reported from clinical trials. Box represents median efficacy with minimum and maximum efficacy range.

Efficacy Varies with Days of Therapy ($pE_n$)

Efficacy rates published in clinical studies represent those of the compliant patients since the majority of clinical trials excluded patients for protocol violations, including noncompliance. Noncompliance does not equate to treatment failure, but the cure rate for a person who completes only 1 day of a 7-day regimen is not equal to the cure rate for a person completing 6 of 7 days of therapy. Dose ranging studies would be useful in estimating this information; however, published information assessing the response of patients to the same dosage and treatment durations of less than 1 week is limited to one study that evaluated miconazole 2% vaginal cream.[79] Similar information was requested from manufacturers of other products and was not available for release. Since regimens of equal duration are considered to have equal efficacy, all 7 day regimens are assumed to have similar success rates if a person completes a given day of a regimen, but does not continue therapy. The efficacy of each day of the 3-day regimens was estimated using the same method (Figure 4).

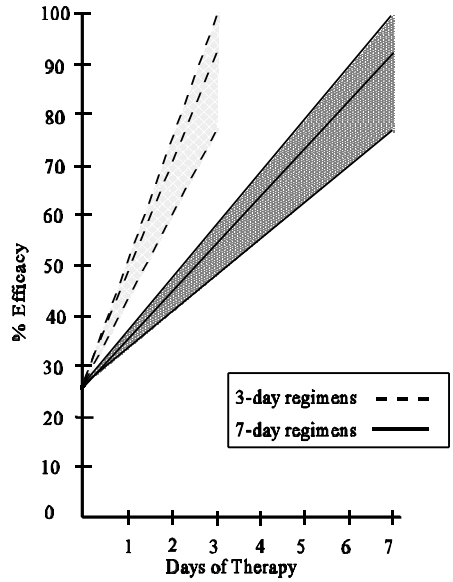


**Figure 4.**—Plot for determining efficacy ranges for a given day of treatment for 3-day and 7-day regimens. The y-intercept represents the spontaneous cure rate. The minimum and maximum efficacy data were derived from clinical trials. Intermediate points were derived from a dose-response study,[79] and a best fit line was determined.

Compliance ($pC_n$)

Compliance rates for single day regimens were set at 98%. Unless a regimen is administered under direct supervision, assuming 100% compliance rates would be faulty, since some patients never fill or pick-up prescriptions.[80] Accurate compliance information is difficult to obtain. No published studies are available evaluating compliance with vaginal preparations for the treatment of VVC. Additionally, compliance information is not readily available in clinical trials,

since the number of patients excluded from the efficacy analysis for noncompliance is not outlined. The best information on compliance was obtained from a pharmaceutical company post-marketing survey of more than 1,000 patients. The survey determined the percent of women completing a given day of a 7-day regimen (written communication, Schering-Plough Medical Information Department, April 1995). The information obtained from this survey was applied to the 3-day regimen, assuming that if a given percent of patients could comply with 3 or more days of a 7-day regimen, they should be able to complete a 3-day regimen.

**Table 2.**—Variables and sensitivity ranges for vulvovaginal candidiasis model.

| Variable | Baseline Value | Range | Reference |
|---|---|---|---|
| Cost of follow-up labs (vaginal pH, NS or wet prep, KOH prep) (cFLA) | $2.00 | $0.50 - 4.00 | Clinical consultant panel* |
| Cost of provider visit (cMDV) | $31.25 (15 min) | $23.09 - 41.25 (10 - 20 min) | CMAC 1993† |
| Average hourly wage of active duty females (cW) | $9.50 | $9.00 - 10.00 | DOD |
| Hours of work lost to return to MD due to drug failure (HR) | 4 hours | 2 - 6 hours | Clinical consultant panel* |
| Probability of active duty female (pADF) | 8.4% | Not varied | Defense Medical Information System, FY 1994 |
| Probability of concomitant infection (pCI) | 4.9% | 2 - 26.2% | 8,14,18,22-24 |
| Prevalence of vaginal candidiasis (Pr) | 24% | 11.9 - 49% | 5,8,13-20 |
| Probability of return visit (pRV) | 50% | Not varied | Clinical consultant panel* |
| Probability of spontaneous resolution of symptoms in a patient not infected with *Candida* (pSR) | 25% | 4.8 - 29.4% | 25,26,28-34 |
| Probability of vulvar involvement (pVI) | 72% | 4 - 72% | 37,61,81, Uniformed Services Prescription Database |
| Sensitivity of a clinical diagnosis ($Se_{CD}$) | 77.35% | 73.7 - 81% | 17,21 |
| Specificity of a clinical diagnosis ($Sp_{CD}$) | 80.5% | 68.9 - 92.1% | 17,21 |
| Compliance if patient takes only *n* day(s) of therapy and does not continue for the full course of treatment | | | |
| Compliance, Day 1 of 1 ($pC_{1/1}$) | 98% | 89 - 100% | ‡ |
| Compliance, Day 1 of 3 ($pC_{1/3}$) | 2% | 1 - 3% | ‡ |
| Compliance, Day 2 of 3 ($pC_{2/3}$) | 4% | 3 - 5 % | ‡ |
| Compliance, Day 3 of 3 ($pC_{3/3}$) | 92% | 83 - 100% | ‡ |
| Compliance, Day 1 of 7 ($pC_{1/7}$) | 2% | 1 - 3% | ‡ |
| Compliance, Day 2 of 7 ($pC_{2/7}$) | 4% | 3 - 5 % | ‡ |
| Compliance, Day 3 of 7 ($pC_{3/7}$) | 12% | 10 - 14% | ‡ |
| Compliance, Day 4 of 7 ($pC_{4/7}$) | 7% | 6 - 9% | ‡ |
| Compliance, Day 5 of 7 ($pC_{5/7}$) | 7% | 6 - 9% | ‡ |
| Compliance, Day 6 of 7 ($pC_{6/7}$) | 7% | 6 - 9% | ‡ |
| Compliance, Day 7 of 7 ($pC_{7/7}$) | 58% | 47 - 69% | ‡ |
| Efficacy if patient takes only *n* day(s) of therapy and does not continue for the full course of treatment | | | |
| Efficacy, Day 1 of 1 ($pE_{1/1}$) | 93% | 77 - 99% | Figures 3 & 4 |
| Efficacy, Day 1 of 3 ($pE_{1/3}$) | 49% | 43 - 51% | " |
| Efficacy, Day 2 of 3 ($pE_{2/3}$) | 71% | 60 - 75% | " |
| Efficacy, Day 3 of 3 ($pE_{3/3}$) | 93% | 77 - 99% | " |

| Variable | Baseline Value | Range | Reference |
|---|---|---|---|
| Efficacy, Day 1 of 7 ($pE_{1/7}$) | 36% | 34 - 37% | Figures 3 & 4 |
| Efficacy, Day 2 of 7 ($pE_{2/7}$) | 47% | 41 - 47% | " |
| Efficacy, Day 3 of 7 ($pE_{3/7}$) | 55% | 48 - 58% | " |
| Efficacy, Day 4 of 7 ($pE_{4/7}$) | 61% | 55 - 68% | " |
| Efficacy, Day 5 of 7 ($pE_{5/7}$) | 73% | 63 - 78% | " |
| Efficacy, Day 6 of 7 ($pE_{6/7}$) | 83% | 70 - 89% | " |
| Efficacy, Day 7 of 7 ($pE_{7/7}$) | 93% | 77 - 99% | " |

* Clinical consultant panel consisted of a family practice physician, an obstetrics and gynecology physician, and an obstetrics and gynecology nurse practitioner.
† CMAC = CHAMPUS Maximum Allowable Charge
‡ Written communication, Schering-Plough Medical Information, April 1995.

***Costs of Care***

Costs associated with the management of vulvovaginal candidiasis are divided into four categories: (1) treatment; (2) failure; (3) adverse effects; and (4) loss of work. Costs encountered are based on a review of the literature and current clinical practices. Drug acquisition prices to the government as of May 28, 1996, were used. Other costs were obtained from CHAMPUS Maximum Allowable Charges and Medicare reimbursements.

Cost of Treatment [cA + cLA + (cTA × pVI)]

Drug cost (cA) is included for treatment of all patients. The model assumes a prescription for medication is provided to the patient, along with instructions to return to the clinic if symptoms have not resolved after treatment (Table 1, Figure 2). Prescription and OTC medications are treated the same in the model since they are assumed to be dispensed from the MTF pharmacy. The model starts with the assumption the patient has a clinical diagnosis of vulvovaginal candidiasis. The initial provider visit cost and initial diagnostic tests, such as normal saline or KOH preparations, or cultures, are not included, since these are constant across all regimens.

The costs of laboratory tests (cLA) required prior to prescribing a medication were considered for the analysis. For example, a pregnancy test may be necessary if the patient's pregnancy status cannot be determined from the clinical history, and the drug carries a Pregnancy Category C rating. Additionally, none of the imidazole or triazole preparations are recommended for use during the first trimester of pregnancy.[7,82] The cost of a pregnancy test is not included in the analysis since the clinical history and current birth control practices can exclude the possibility of pregnancy in the majority of patients. In patients whom pregnancy status cannot be determined, the use of regimens approved for use in pregnancy is suggested (Table 1).

Medications for the treatment of VVC are available in several different dosage forms, including creams, ointments, vaginal suppositories and tablets, and oral tablets. Because vaginal candidiasis may be complicated with vulvar involvement in some patients (pVI), the ability of a product to treat concomitant vulvar infections was considered. Cream and ointment preparations can be applied externally if required, while other preparations would require an additional topical antifungal cream to treat vulvar involvement. Similar efficacy rates are assumed for vaginal and topical creams with respect to treating vulvar involvement. Miconazole 2% topical cream was selected for this analysis because it is the lowest priced topical agent (cTA). Clotrimazole 500 mg vaginal tablets and miconazole 200 mg vaginal suppositories are available in combination kits with a topical cream, thus the additional cost for a topical cream is not included for these two products. The miconazole 100 mg suppositories are also available in a combination kit; however, these kits are not available through federal suppliers, so the cost of the topical cream is included for this product. All other oral tablets, vaginal tablets, or suppositories include the cost of a topical cream for the percentage of women with concomitant vulvar involvement.

Cost of Failure [(1 - pEff) × (cMDV + cFLA) × pRV]

We assumed the costs of failure are incurred by patients not responding to treatment (1 - pEff). Cost of failure included a 15 minute provider visit (cMDV) and additional diagnostic tests (vaginal pH, normal saline preparation, and KOH preparation) (cFLA) to determine if a *Candida* infection is actually present. The diagnostic tests require

additional practitioner time to conduct the tests, but the actual cost of the products needed to conduct the tests (i.e., slides, slide covers, normal saline, potassium hydroxide, and pH strips) represents a minimal cost to the system. The cost of these diagnostic tests is set at $2.00. The practitioner time for conducting these tests is included in the practitioner visit. Ideally, failure costs should be applied to all patients considered to be treatment failures. However, VVC is a self-limiting disease[10,27] and with the availability of OTC treatments, not all patients will return to the clinic for additional treatment. The model includes a factor to account for the probability of the patient returning to clinic (pRV).

Cost of Adverse Events

The major side effect associated with the vaginal treatment regimens is vulvovaginal irritation.[3,12] Unfortunately, the nature of VVC makes it difficult to distinguish the adverse effect from the disease process. Oral fluconazole is commonly associated with gastrointestinal symptoms, such as nausea, abdominal pain, and diarrhea. These symptoms are usually of mild to moderate severity.[83] Because the adverse effects of these medications are self-limiting, the costs to the DOD are negligible and are not included in the analysis. Few patients discontinued the drug because of adverse effects in the clinical trials.[22,34-39,41-52,55-57,59-64,66-71,73,74] The discontinuation rate due to side effects is reflected in the patient compliance.

Cost of Loss of Work [HR × cW × (1 - pEff) × pADF × pRV]

If the payer of the health care benefits is also the employer of some or all of the patients, costs due to loss of work are important. The DOD is the health care payer for active duty personnel (employees), dependents of active duty personnel, and retired persons and their dependents. Because of the payer perspective in this model, as opposed to a societal perspective, a cost for loss of work or productivity (cW) is encountered when treatment fails (1 - pEff) for female active duty personnel (pADF), and they return to the practitioner for further evaluation. We assumed an average of 4 hours of duty time was lost to return to the practitioner (HR). Loss of work or productivity costs of non-active duty personnel are not included since this lost productivity is not a cost to the military. As with the cost of failure, if treatment fails for female active duty personnel, but they do not return to the clinic, there is no cost to the system. The model includes a factor to account for the probability of female active duty personnel returning to clinic (pRV).

*Assumptions*

Assumptions included in the vulvovaginal candidiasis model are outlined below.

- The analysis is conducted from the perspective of the DOD as payer of the health care benefits to DOD beneficiaries and employer of active duty female members.
- Women in the MHSS between 15 and 65 years of age were considered the target population.
- Pregnant women were not included in the analysis; these patients may require longer duration of therapy or repeated treatment courses during their pregnancy.[2]
- Treatment regimens were evaluated for uncomplicated, episodic VVC. Recurrent VVC (3 or more episodes annually)[2] or chronic VVC are not included in the analysis
- The decision to treat a patient for VVC is largely based on clinical signs and symptoms. Simple diagnostic tests, such as a 10% potassium hydroxide preparation or a normal saline preparation for microscopic examination, may be conducted routinely in some settings. Cultures are rarely, if ever, done for diagnosis of VVC. Initial laboratory testing and provider visit are not included in the model.
- Pregnancy testing is not included as an initial laboratory cost.
- A clinical diagnosis of VVC occurs in patient groups: (1) patients with *Candida* infection (true-positive diagnosis); (2) patients with *Candida* and concomitant infections; and (3) patients with signs and symptoms consistent with *Candida* infection, but without *Candida* infection (false-positive diagnosis).
- A prescription for a drug product is provided to the patient along with instructions to return to clinic if symptoms have not resolved. Both prescription and over-the-counter (OTC) medications are assumed to be dispensed from the MTF pharmacy.
- If a patient has vulvar involvement, the cost of a topical cream is included for drugs available as suppository or oral formulations. If a combination package with the suppository and a topical cream is available through federal sources, this package cost is also included in the analysis.
- Similar efficacy rates are assumed for vaginal and topical creams with regard to treating vulvar involvement.
- Adverse effects to medications for treatment of VVC are minimal and are not included in the analysis.

- Lost productivity costs are included only for active duty personnel since they are employed by the health care payer (DOD). An average of 4 hours (half a day) of duty time is assumed to be lost for additional follow-up.
- Efficacy of a treatment regimen is based on a short-term clinical cure, defined as significant improvement or complete resolution of the clinical signs and symptoms of VVC between 5 and 10 days after the start of treatment.
- All medications have equal efficacy when used for the recommended treatment duration; all regimens were assumed to have a median efficacy of 92.85% at the end of a full treatment course.
- Patients not compliant with the full course of therapy may have a clinical cure. Compliance was assumed to be equivalent for oral and vaginal preparations.
- Therapy failure for patients with *Candida* and concomitant infection is assumed to occur due to the concomitant infection.
- Not all patients with a treatment failure will return to clinic for additional treatment. We assumed that 50% of patients with a treatment failure would incur additional costs to the system.

**Results**

Baseline Analysis

We determined the cost per clinical cure for vulvovaginal candidiasis after one course of antifungal treatment. Clotrimazole 500 mg vaginal tablet, 1-day regimen, demonstrated the lowest cost per clinical cure ($20.03). The clotrimazole 500 mg tablet kit (vaginal tablet with a topical cream) was $21.46 per clinical cure. The second regimen in the baseline analysis was the clotrimazole 200 mg vaginal tablet, 3-day regimen ($24.35) followed by single dose fluconazole 150 mg oral tablet ($24.51) as the third regimen (Table 3).

Sensitivity Analysis

Individual variables were changed over the ranges described in Table 2 to determine the effect of single variables on the analysis results (univariate sensitivity analysis). When individual values were varied over these ranges, clotrimazole 500 mg × 1 day retained the lowest cost-effectiveness ratio. Univariate sensitivity analysis demonstrated that for the 3-day regimen of clotrimazole 200 mg to be more cost-effective than the 1-day regimens, the relative effectiveness ($pE_n \times pC_n$) of the 1-day regimens would have to decrease by 10% (i.e., from 89% to 79%), a situation unlikely to occur.

Prevalence of the disease was the variable with the largest contribution to the variability of the model. As the prevalence was decreased (24% to 12%), the clinical diagnostic accuracy (pCCD) also decreased (56% to 35%), thus the cost per clinical cure increased. This effect occurs because more patients are being treated for *Candida* infections who do not have disease (false-positives). The opposite situation occurs when the prevalence is increased. Because the prevalence of disease was a constant variable across all drug regimens, the rank order of the treatments did not change with a change in the prevalence. Similarly, when the specificity or sensitivity of the clinical diagnosis were increased, the diagnostic accuracy increased, and the cost per clinical cure decreased since more patients with disease are being treated (true-positives). Again, the overall rank order of the drug regimens remained unchanged with these changes.

A Monte Carlo analysis also was performed to measure the effects of simultaneous changes in multiple assumptions (multivariate sensitivity analysis). The top eight regimens in the baseline analysis remained the top eight regimens after the Monte Carlo simulation of 1000 trials. Clotrimazole 500 mg vaginal tablet remained the most cost-effective regimen. Terconazole 0.8% vaginal cream × 3 days, the ninth ranked regimen in the baseline analysis, and terconazole 80 mg, 3-day vaginal suppositories, the tenth ranked regimen at baseline, switched places after the Monte Carlo analysis to tenth and ninth, respectively. Similarly, tioconazole 6.5% vaginal ointment and terconazole 0.4% 7-day vaginal cream switched places after the Monte Carlo analysis to thirteenth and twelfth, respectively (Table 3, Figure 5).

**Discussion**

Our pharmacoeconomic model used the best available data to compare the cost-effectiveness of the antifungal drug therapies for the treatment of uncomplicated vulvovaginal candidiasis in DOD beneficiaries. Clotrimazole 500 mg single-dose vaginal tablet was the regimen of choice in both the baseline analysis and the Monte Carlo analysis. These results specifically apply to women with a clinical diagnosis of uncomplicated VVC in a primary care setting. The analysis does not address and is not necessarily generalizable to patients with complicated VVC, pregnant patients, or patients with recurrent or chronic VVC who may require additional follow-up and care from an obstetrician/gynecologist or an infectious disease specialist.

**Table 3.—**Mean cost-effectiveness (C-E) (cost per clinical cure) after Monte Carlo analysis.

| Rank after Monte Carlo Analysis | Drug Regimen | Average C-E after Monte Carlo Analysis | 95% Confidence Intervals | Rank at Baseline |
|---|---|---|---|---|
| 1 | Clotrimazole 500 mg vaginal tab × 1 day | $24.52 | 24.06 - 24.98 | 1 |
| | Clotrimazole 500 mg vaginal tab kit × 1 day* | $26.53 | 26.05 - 27.01 | |
| 2 | Clotrimazole 200 mg vaginal tab × 3 days | $28.87 | 28.38 - 29.36 | 2 |
| 3 | Fluconazole 150 mg oral tab × 1 day | $29.52 | 29.01 - 30.03 | 3 |
| 4 | Clotrimazole 1% vaginal cream × 7 days | $30.83 | 30.34 - 31.32 | 4 |
| 5 | Miconazole 2% vaginal cream × 7 days | $31.79 | 31.29 - 32.28 | 5 |
| 6 | Clotrimazole 100 mg vaginal tab × 7 days | $33.61 | 33.10 - 34.13 | 6 |
| 7 | Miconazole 100 mg vaginal suppository × 7 days | $33.70 | 33.18 - 34.21 | 7 |
| 8 | Butoconazole 2% vaginal cream × 3 days | $39.66 | 39.06 - 40.26 | 8 |
| 9 | Terconazole 80 mg vaginal suppository × 3 days | $40.34 | 39.73 - 40.94 | 10 |
| 10 | Terconazole 0.8% vaginal cream × 3 days | $40.55 | 39.95 - 41.16 | 9 |
| 11 | Miconazole 200 mg vaginal suppository × 3 days kit* | $41.41 | 40.79 - 42.02 | 11 |
| | Miconazole 200 mg vaginal suppository × 3 days | $42.12 | 41.50 - 42.74 | |
| 12 | Terconazole 0.4% vaginal cream × 7 days | $44.52 | 43.91 - 45.14 | 13 |
| 13 | Tioconazole 6.5% vaginal ointment × 1 day | $44.78 | 44.12 - 45.44 | 12 |

* Clotrimazole 500 mg vaginal tablet kit contains the vaginal tablet plus a tube of clotrimazole topical cream; miconazole 200 mg vaginal suppository kit contains 3 vaginal suppositories plus a tube of miconazole topical cream.

The payer perspective, as used in this model, focuses primarily on costs to the health system of interest. Thus, in this model as applied to the DOD, costs incurred from patient self-treatment or loss of work for non-active duty patients are not included. For this model to apply from a societal perspective, both self-treatment costs and provider-directed treatment costs should be addressed. Additionally, all loss of work costs should be included in the societal perspective to provide the total cost of health care.

As previously mentioned, we assumed patients would be provided with a prescription for both legend and OTC antifungal agents to be filled at the MTF pharmacy at no cost to the patient. This assumption may overestimate the cost incurred by the system, since some patients may go out on their own and purchase an OTC product instead of visiting a provider or waiting to have a prescription filled at the MTF pharmacy.

The clinical efficacy of each regimen was obtained from the medical literature. Only two published comparative trials reported significant differences in the efficacy of the antifungal agents.[52,75] In one study, oral fluconazole (n=121) resulted in higher cure rates compared to vaginal econazole (n=114) (econazole vaginal tablet not available in the U.S.). The difference was significant in the 1-tail Fisher's exact test (p=0.046), but not in the 2-tail test (p=0.071).[52] In the second study, oral fluconazole (n=72) demonstrated significantly lower cure rates than vaginal clotrimazole 500 mg (n=82) (p=0.027). When patients with clinical improvement are included with those that are cured, the efficacy rates for fluconazole and clotrimazole are similar (91% vs. 92%, respectively).[75] Because no significant differences in efficacy could be identified from the clinical trials, all medications were assumed to have equal efficacy at the end of a full treatment course. A median efficacy, as compiled from all the clinical trials, was used as the point estimate.

Clinical studies of VVC included only patients who were highly compliant, thus overestimating the true effec-tiveness of therapy. An adjustment for patient compliance provides an estimate of the true effectiveness. In the absence of published information on compliance with vaginal products, the results of a pharmaceutical company sponsored post-marketing survey were used. Post-marketing surveys are limited by their reliance on patient recall and the absence of an objective observer.

Additionally, we assumed the compliance would not differ with the use of an oral tablet or a vaginal product. The argument could be made that oral dosage forms would provide improved patient compliance, but in this case, because fluconazole is a single dose regimen, compliance is

not a major factor. The compliance information included in the analysis reflected patient use of vaginal preparations from survey information. Studies are needed to better determine patient compliance with vaginal products.

A specific concern in the active duty female is the use of vaginal preparations in deployment situations. Vaginal creams and tablets have a level of inconvenience that is not observed with fluconazole oral tablets. This factor was not incorporated into the model because of the specific nature of the issue. Fluconazole ranked fourth overall ($29.52/clinical cure) in the analysis. When assessing only the 1-day regimens, fluconazole is the most-cost-effective 1-day regimen after clotrimazole 500 mg. Because of its convenience for active duty females in deployment situations, fluconazole should be considered as an additional therapy in this specific situation.

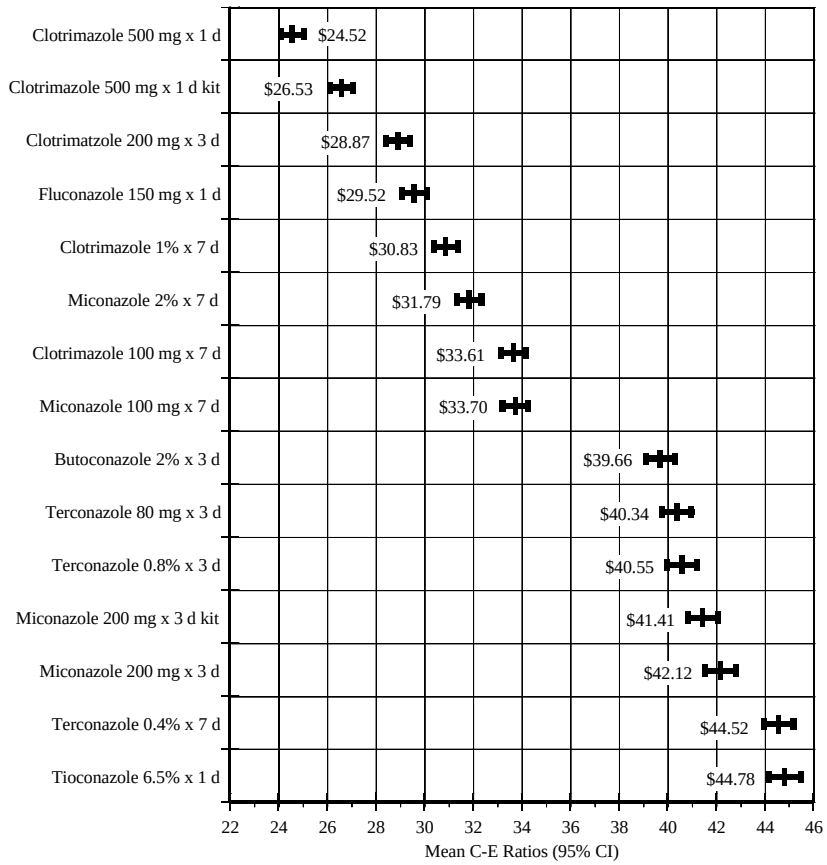


**Figure 5.—**Mean cost-effectiveness ratios (mean cost per clinical cure) with 95% confidence intervals based on Monte Carlo analysis results.

Diagnostic methods also differ between the clinical trials and clinical practice. The clinical trials enrolled only patients with mycologic evidence of vaginal candidiasis. In the model, we employ a lower level of diagnostic accuracy that is associated with a clinical diagnosis. As diagnostic accuracy increases, the number to treat decreases since fewer patients who do not have disease are being treated (false-positives). The cost-effectiveness ratios (cost per clinical cure) decrease because more patients who are being treated actually have disease (true-positives).
If improved diagnostic accuracy is achieved by using an additional diagnostic test, such as a latex agglutination test, the additional cost of the test must be included. A median sensitivity of 83.9% and a median specificity of 97.1% for latex agglutination tests[17,21,84-86] would provide a 90% probability of a correct diagnosis compared to the 56% rate in the baseline analysis. As the probability of correct diagnosis increases, the probability of a cure in patients without *Candida* deceases since fewer patients are considered to be in this category. To be cost-effective compared to a clinical diagnosis without additional testing, the model predicts the latex agglutination test should cost the DOD less than $4.25 per test.

The model is limited by the data included for the patient group with *Candida* and a concomitant infection. We assumed all patients with a concomitant infection were considered treatment failures since the initial treatment was for candidiasis, not the concomitant infection. In other words, we assumed the treatment of the candidiasis may have unmasked the concomitant infection, thus the patient returned for additional treatment. The data included in the model represent the prevalence of concomitant infections among patients with VVC.[8,14,18,22-24] Some of these patients may be symptom-free after using an antifungal preparation, while others will require additional treatment. However, no data are available evaluating the cure rates in patients with concomitant infections, thus the percentage of patients who require additional treatment is not known.

In our model, we did not differentiate between specific *Candida* species responsible for vaginitis. *Candida albicans* accounts for 80 to 90% of all cases of VVC; however, recent reports suggest the incidence of infections due to non-*albicans Candida*, such as *C (Torulopsis) glabrata*, is rising.[3,9,87,88] This change in pathogens is important when considering the spectrum of activity of current imidazole and fluconazole treatment regimens. These agents are not as active against non-*albicans*

*Candida* species compared to *C albicans*.[3,9,83,87,88] Terconazole, the only topical triazole agent, has a broad spectrum of activity against non-*albicans Candida* species.[3,9] Many clinicians do not use cultures for the initial diagnosis of vaginal *Candida* infections, and thus may not treat for a non-*albicans Candida* infection initially. Additionally, only a few clinical trials eval-uating antifungal regimens report *Candida* species[36,38,40,51,61,66,70,73] other than *C albicans*. Finally, the consensus of the consultant panel (obstetrician/gynecologist, family practitioner, OB/GYN nurse practitioner) was that at the evaluation of an initial episode of vaginal candidiasis, non-*albicans Candida* is not a significant problem; thus, we did not differentiate between these species in the model. Additional clinical trials to evaluate the effectiveness of each antifungal agent for different *Candida* species are needed to fully evaluate the impact of this factor. The cost-effectiveness rankings of drug therapies could change as the incidence of non-*albicans Candida* changes.

Our model included only 1-, 3-, or 7-day regimens currently used for the treatment of VVC. Nystatin was the first antifungal regimen available for the treatment of VVC.[55] Although nystatin is still available, it is not commonly used since the newer imidazole and triazole agents have been developed. Additionally, nystatin requires a 14 day treatment regimen and has a lower efficacy compared to the newer agents.[2,7,10] Poor patient compliance with a 14-day regimen and a low efficacy would contribute to a lack of cost-effectiveness for nystatin if it were included in the analysis.

Both ketoconazole[10,39,41,89-92] and itraconazole[10,73-75,93-97] have been investigated for the treatment of acute and recurrent VVC. Neither of these agents are approved by the Food and Drug Administration for these indications,[12] nor are they extensively used acutely in the primary care setting. The usual dosage of ketoconazole for acute vulvovaginal candidiasis is 400 mg daily orally for 5 days.[10,41,89,91] Itraconazole 200 mg daily orally for 3 days is the most commonly reported dosage for acute therapy.[10,73,94-96] If these drugs achieve more widespread use for acute treatment of VVC, they must be included in future cost-effectiveness analyses.

**Tri-Service Formulary (TSF) Selections**

Based on this analysis, clotrimazole 500 mg single-dose vaginal tablet is the most cost-effective regimen for the treatment of uncomplicated, episodic vulvovaginal candidiasis ($24.52/clinical cure), and thus is added to the TSF. For patients with vulvar involvement, miconazole 2% topical cream (15 gm or 30 gm tube) should also be provided. Miconazole 2% topical cream was selected since it had the lowest drug acquisition cost of the available topical antifungal agents, and thus is added to the TSF. If clotrimazole 500 mg single dose vaginal tablet does not provide a cure, the diagnosis should be reconsidered, and if candidiasis is diagnosed or still suspected, the patient could repeat the regimen or use the next appropriate regimen. Fluconazole, although ranked fourth overall ($29.52/clinical cure), has considerable conven-ience for active duty females in deployment situations, and thus, should be added to the D-Day list of medications for deployment, along with the TSF selection of clotrimazole 500 mg. Fluconazole is **not** added to the TSF.

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# Treatment Algorithm for Vulvovaginal Candidiasis

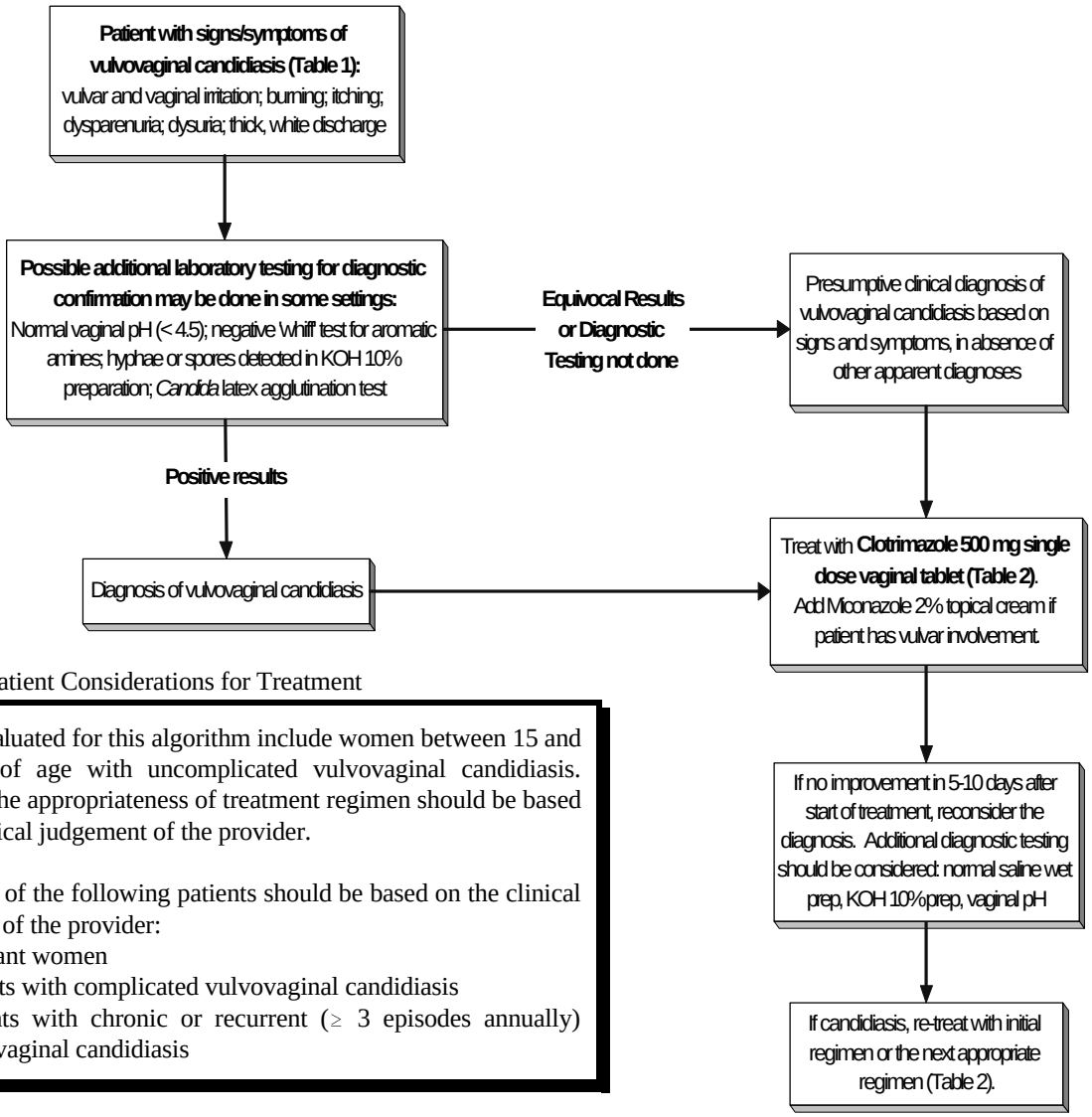


**Table 1.—**Patient Considerations for Treatment

Patients evaluated for this algorithm include women between 15 and 65 years of age with uncomplicated vulvovaginal candidiasis. However, the appropriateness of treatment regimen should be based on the clinical judgement of the provider.

Treatment of the following patients should be based on the clinical judgement of the provider:

1.) pregnant women
2.) patients with complicated vulvovaginal candidiasis
3.) patients with chronic or recurrent (≥ 3 episodes annually) vulvovaginal candidiasis

**Table 2.—**Rank of Drug Regimens by Average Cost-Effectiveness

| Rank | Drug Regimen | Cost per Clinical Cure (Average C-E) |
|---|---|---|
| 1 | Clotrimazole 500 mg vaginal tab × 1 day | $24.52 |
| | Clotrimazole 500 mg vaginal tab kit × 1 day* | $26.53 |
| 2 | Clotrimazole 200 mg vaginal tab × 3 days | $28.87 |
| 3 | Fluconazole 150 mg oral tab × 1 day | $29.52 |
| 4 | Clotrimazole 1% vaginal cream × 7 days | $30.83 |
| 5 | Miconazole 2% vaginal cream × 7 days | $31.79 |
| 6 | Clotrimazole 100 mg vaginal tab × 7 days | $33.61 |
| 7 | Miconazole 100 mg vaginal suppository × 7 days | $33.70 |
| 8 | Butoconazole 2% vaginal cream × 3 days | $39.66 |
| 9 | Terconazole 80 mg vaginal suppository × 3 days | $40.34 |
| 10 | Terconazole 0.8% vaginal cream × 3 days | $40.55 |
| 11 | Miconazole 200 mg vaginal suppository × 3 days kit* | $41.41 |
| | Miconazole 200 mg vaginal suppository × 3 days | $42.12 |
| 12 | Terconazole 0.4% vaginal cream × 7 days | $44.52 |
| 13 | Tioconazole 6.5% vaginal ointment × 1 day | $44.78 |

* Clotrimazole 500 mg vaginal kit contains the vaginal tablet plus a tube of clotrimazole topical cream; miconazole 200 mg vaginal suppository kit contains 3 vaginal suppositories plus a tube of miconazole topical cream. All other tablet/suppository regimens include the cost of miconazole 2% topical cream for those patients with vulvar involvement.

# DRUG USAGE EVALUATION MONITORING FORM

DISEASE STATE Vulvovaginal candidiasis DRUG _____

SURVEY PERIOD: FROM: _____ TO: _____

COLLECTED BY: _____ DATE OF COLLECTION: _____

ATTENDING PHYSICIAN _____ SERVICE _____

PATIENT NAME _____ SSN _____ AGE _____

SEX _____ WEIGHT _____ ALLERGIES _____

| ELEMENT | STD* | MET STD | COMMENT |
|---|---|---|---|
| 1. Patient improvement as evidenced by:<br>a. Clinical cure or improvement of signs/symptoms of vulvovaginal candidiasis after treatment with antifungal regimen (resolution of vulvar and vaginal irritation, burning, itching, dysparenuria, dysuria, or thick, white discharge).<br>b. Adverse events reported through the ADR reporting system. | 90%<br>100% | Y/N | Medical record reflects adverse events reported through MTF ADR reporting system. |
| 2. If no improvement noted 5 to 10 days after start of treatment,<br>a. additional diagnostic testing considered (potassium hydroxide 10% preparation, normal saline wet prep, vaginal pH).<br>b. patient factors considered (pregnant patient, chronic/recurrent disease, underlying complication, such as HIV infection or diabetes mellitus, etc.) | 100%<br>100% | Y/N | |
| 3. Less than optimal outcome (select category if present):<br>a. Inappropriate drug regimen.<br>b. Non-compliant behavior by patient.<br>c. Patient allergy/idiosyncratic reaction.<br>d. Complication unrelated to drug therapy.<br>e. Inappropriate monitoring of pharmacotherapy (i.e., drug-drug or drug-food interactions). | 5% | Y/N | |

* Standard to be adjusted by MTF Pharmacy & Therapeutics / Drug Utilization Evaluation Committee.

## Tri-Service Formulary Quick Reference Guide

**Antimicrobials / Antifungals**
*amoxicillin oral suspension and caps
*Bactrim™/Septra® susp and tabs
*dicloxacillin oral
*doxycycline 100 mg caps
*erythromycin oral suspension and tabs or caps
*erythromycin/sulfisoxazole susp
*griseofulvin 125 mg tabs
*isoniazid 300 mg tabs
*metronidazole 250 mg tabs
*nystatin oral suspension
*penicillin VK susp and 250 mg tabs
*rifampin 300 mg caps
*tetracycline 250 mg caps

**Antibiotics-EENT**
*Cortisporin® Otic Suspension
*gentamicin ophth. soln. 0.3%
*Neosporin® Ophth. Solution
*sulfacetamide ophth. oint. 10%

**Antivirals**
acyclovir 200 mg caps

**Anthelmintics**
mebendazole 100 mg chew tabs

**Antiulcer Drugs**
*amoxicillin oral
*bismuth subsalicylate 262 mg tabs
*metronidazole 250 mg tabs
*tetracycline 250 mg caps

**GERD Agents**
cisapride 20 mg tabs
omeprazole 20 mg caps

**Other GI Agents**
*dicyclomine tabs or caps
*Donnatal® tabs
*sulfasalazine 500 mg tabs

**Anti-diarrheals**
*loperamide 2 mg tabs or caps

**Genitourinary Agents**
*oxybutynin 5 mg tabs
*phenazopyridine 100 mg tabs

**Gout Agents**
*allopurinol tabs
*probenecid 500 mg tabs

**Muscle Relaxants**
*diazepam 5 mg tabs
*methocarbamol 500 mg tabs

**Oral Corticosteroids**
*prednisone 5 & 20 mg tabs
prednisone oral soln 5 mg/5 mL
prednisolone oral soln 15 mg/5 mL

**Nasal Corticosteroids**
*beclomethasone nasal inhaler

**Asthma Agents**
*albuterol oral inhaler
flunisolide oral inhaler
triamcinolone oral inhaler
*theophylline liquid 80 mg/15 mL
SloBid™ Gyrocaps 50, 200, 300 mg

**Antihistamines / Decongestants**
*Actifed® tabs
*chlorpheniramine 4 mg tabs
*chlorpheniramine syrup
*Dimetapp® Elixir
*Dimetapp® Extentabs
*diphenhydramine caps
*diphenhydramine syrup
*hydroxyzine syrup
*hydroxyzine tabs
*oxymetazoline nasal spray
*pseudoephedrine 30 mg tabs

**Anticonvulsants**
Dilantin® Infatabs 50 mg
Dilantin® Kapseals 100 mg
*phenobarbital elixir 20 mg/5 mL
*phenobarbital 30 mg tabs
*primidone 250 mg tabs
†Tegretol® 200 mg tabs

**Anticoagulants**
warfarin 5 mg tabs

**Diuretics**
*furosemide 40 mg tabs
*hydrochlorothiazide tabs
*Maxzide® tabs
*spironolactone 25 mg tabs

**Vasodilators**
*isosorbide dinitrate 10 mg tabs
nitroglycerin sublingual tabs

**Lipid Lowering Agents**
colestipol powder
*niacin tabs
pravastatin 10 mg, 20 mg, 40 mg tabs

**Hypotensive / Cardiac Drugs**
*atenolol tabs
*clonidine tabs
†Lanoxin® 0.25 mg tabs
lisinopril tabs
*propranolol 10 & 40 mg tabs
*quinidine gluconate 324 mg tabs
*quinidine sulfate tabs
terazosin tabs
*verapamil long-acting tabs

**Electrolyte Replacement**
*potassium chloride slow release tabs or caps

**Diabetic Agents**
*human insulin, regular & NPH

**NSAIDS / Analgesics**
*acetaminophen drops, elixir, and 325 mg tabs
*aspirin, enteric-coated 325 mg tabs
*ibuprofen susp and 400 mg tabs
*indomethacin 25 mg caps
*Tylenol #3® tabs

**Migraine Agents**
*Cafergot® tabs
*Fiorinal® tabs
*Midrin® caps

**Attention Deficit / Narcolepsy Agents**
*methylphenidate 10 mg tabs
*methylphenidate sustained release 20 mg tabs

**Contraceptives**
LoOvral®
*Norinyl 1+50®, Ortho-Novum 1/50®
*Ortho-Novum 1/35®, Norinyl 1+35®
Ortho-Novum 7/7/7®
Ovral®
Triphasil®/Tri-Levlen®

**Estrogens / Progestins**
conjugated estrogens 0.625 mg tabs
conjugated estrogen vaginal cream
*medroxyprogesterone 10 mg tabs

**Thyroid / Antithyroid Agents**
*propylthiouracil 50 mg tabs
†Synthroid® 100 mcg (0.1 mg) tabs

**Topical Agents**
*bacitracin ointment
*hydrocortisone 1% cream
*miconazole 2% topical cream
Sebutone® shampoo
*Selsun® shampoo

**Vaginal Antifungal Agents**
clotrimazole 500 mg vaginal tab

**Vitamins & Minerals**
*ferrous sulfate concentrated soln. 125 mg/mL
*ferrous sulfate 325 mg tabs
*pyridoxine 50 mg tabs

**Miotics**
*pilocarpine ophth. solution

**Miscellaneous**
insect sting kit
InspirEase® spacer

***generic products are available***
***†DMSB sole source item***

***Brand names are included for example only and are not meant to imply the recommendation of a specific product except for those products designated as sole source items by the Defense Medical Standardization Board.***

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